REMARKS / ARGUMENTS

A telephonic interview was conducted over this case on April 4th, 2006. A statement of the substance of this interview is provided below. As a result of this interview, the finality of the Final Office Action mailed February 22, 2006 was withdrawn, and a Supplemental, Non-Final Office Action was mailed May 25, 2006.

The Supplemental, Non-Final Office Action, was received and reviewed. This response addresses all concerns of the Examiner in this Supplemental Office Action.

Claims 1 through 34 are pending in the Application, and claims 1 through 15 are withdrawn from consideration as being directed to a non-elected invention. Claims 16 through 34 were rejected. Claims 30 and 34 are being amended as shown above.

Applicants respectfully request reconsideration of the amended Application by the Examiner in view of the following remarks and arguments.

STATEMENT OF THE SUBSTANCE OF THE TELEPHONIC INTERVIEW OF APRIL 4, 2006

A telephonic interview concerning this Application was held on April 4, 2006. Attending were Examiners Louis V. Wollenberger and Doug Schultz, representing the United States Patent and Trademark Office (USPTO); and Herbert L. Ley III and Jay Z. Zhang, representing the Applicants.

Under discussion were the rejections presented in the Final Office Action, mailed February 22, 2006. Specifically, rejections under 35 USC § 112, 2nd paragraph – Definiteness; 35 USC § 112, 1st paragraph – Written Description; and 35 USC § 102(b) – Novelty, in view of Cox *et al., Genes & Development* 12:3715-3727 (1998), were discussed, as was the finality of the Final Office Action.

FINALITY OF THE PREVIOUS OFFICE ACTION

During the telephonic interview, Applicants formally requested reconsideration of the finality of the Final Office Action, mailed February 22, 2006. Applicants' grounds for requesting reconsideration were based on the fact that the Final Office Action issued a 35 USC § 102(b) anticipation rejection citing, for the first time, prior art by Cox *et al.,*(*Genes & Development* 12:3715-3727 (1998)), which, in the opinion of the Applicants, (a) could

have been cited in the previous Office Action, (b) was not necessitated by an amendment, and (c) did not, in fact, anticipate the claimed invention.

Applicants' arguments were deemed persuasive, and Examiners Wollenberger and Schulz agreed that the Office Action mailed February 22, 2006, was prematurely made Final. Consequently, the Examiners indicated that another Office Action would be prepared and mailed, which would withdraw the finality of the preceding Office Action and reopen the prosecution of the Application. Confirmation of this decision was received by Applicants in the form of a telephone call from Primary Examiner Sean McGarry approximately two days after the telephonic interview took place.

CLAIM AMENDMENTS

Claims 30 and 34 have been amended, as shown above, by the deletion of the term "FLAG®." These amendments obviate the rejection under 35 USC § 112, 2nd paragraph.

The amendments should be entered into the record because they neither add new matter to the Application, nor raise new issues that would require further search, and they place the claims in condition for allowance, or, alternatively, in better condition for appeal.

THE REJECTIONS

35 USC § 112, 2nd paragraph – Definiteness:

Claims 30 and 34 stand rejected under 35 USC § 112, 2nd paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As noted above, the amendment of claims 30 and 34 provided herein removes the offending trademark/trade name "FLAG®," thereby obviating the rejection. Applicants respectfully note, however, that the term "FLAG," as used in the context of the detectable peptide tags of the instant invention, has had clear meaning in the art since at least 1994, when Brizzard and colleagues, of the Eastman Kodak Company, taught, in the abstract of a paper published in the widely distributed trade journal *Biotechniques*, that "[t]he FLAG epitope is an eight amino acid peptide (AsnTyrLysAspAspAspAspLys) that is useful for

immunoaffinity purification of fusion proteins." (See Brizzard *et al. Biotechniques* 16(4):730-5, (1994)), abstract, provided herewith as *Exhibit A*.) Despite the clarity of meaning provided by this prior art reference, Applicants acquiesce to the Examiner's request that the offending trademark/trade name be removed from the claims, noting that the subject matter is still covered by the claim under the umbrella a "detectable peptide tag," as recited in claims 28 and 32.

35 USC § 112, 1st paragraph – Written Description:

Claims 16-34 stand rejected under 35 U.S.C. § 112, 1st paragraph for being based upon a specification that allegedly provides insufficient written description of the claimed invention. Over the course of more than 9 pages, the Supplemental Office Action of May 25, 2006 attempts to substantiate this rejection by alleging: (1) the claims are too broad (claiming "any siRNA or shRNA targeting any nucleic acid sequence encoding any detectable peptide tag"), and specification does not allow the skilled artisan to recognize that applicants were in possession of the "the entire genus of universal interfering siRNAs, shRNAs, and expression vectors expressing said siRNAs and shRNAs targeting all possible universal target RNAs;" (2) the specification provides no specific examples of the invention; (3) the specification provides no evidence that the invention has actually been reduced to practice; (4) the claimed invention is a "chemical invention," therefore the specification must provide a "precise definition" of the "detailed chemical structure" (i.e., nucleotide sequence) of the encompassed genus of universal interfering siRNAs and shRNAs targeting the entire genus of universal target RNAs; and (5) the level of unpredictability in the related art is so high as to preclude skilled artisans from envisioning the structures and sequences of any interfering siRNAs and shRNAs, and universal target RNAs that could be in the kits of the claims.

At the outset, Applicants feel that it is important to note the following facts:

1. The claims at issue are NOT drawn towards novel compositions of matter, such as specific siRNAs, specific expression vectors, specific target RNAs, etc., they are, instead, drawn towards **methods** of altering the expression of genes by RNA interference (RNAi) in a plurality of cells or organisms using a universal interfering RNA directed towards a common target RNA in chimeric RNA transcripts (claims 1-

15), and **kits** for practicing the disclosed methods (claims 16-34). Furthermore, the claims under consideration need not rely upon novel compositions of matter for the various claim elements, but, instead, can encompass new combinations of old elements as the means to carry out the methods of the invention.

2. Working embodiments of the claimed invention have been reduced to practice by at least two groups of researchers since the filing of the instant patent application. (*See*, Mangeot *et al*., *Nucleic Acids Res*. 32:e102 (2004), provided to the Office in the IDS filed March 3, 2004; and Campbell and Choy, *Genet. Mol. Res*. 3:282-287 (2004), provided to the Office in the Supplemental IDS filed September 8, 2006.) Both of these embodiments make use of known ("old") elements (i.e., known siRNAs or shRNAs targeting a specific sequence in mRNA encoding enhanced green fluorescent protein, or EGFP – which was specifically disclosed in the specification) to create a functioning embodiment of the instant invention.
3. While the art of RNAi contains some degree of unpredictability, it has proven itself predictable enough to become a standard technique in the field of molecular biology, and is even being used as a means to treat certain human diseases (e.g., wet age-related macular degeneration; *see* http://www.acuitypharma.com). Furthermore, while some experimentation may be required to identify siRNAs that effectively reduce expression of specific genes, such experimentation, which is by no means undue, has definitely not deterred skilled artisans from routinely using RNAi as a tool to study gene function.

The various aspects of the written description rejection will now be discussed.

As a first matter, compliance with the "written description requirement" is a question of fact. For this reason, the MPEP § 2163.04 notes: "The examiner has the initial burden of presenting **by a preponderance of evidence** why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97." (MPEP, 8th Ed. Rev. 3, August 2005, pp. 2100-186-2100-187; emphasis added). MPEP § 2163.04 further instructs:

> In rejecting a claim, the examiner must set forth **express findings of fact** which support the lack of written description conclusion .... **A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description**.

(MPEP, 8th Ed. Rev. 3, August 2005, pp. 2100-187; emphasis added).

Applicants respectfully assert that, in the present case, the Supplemental Office Action of May 25, 2006 fails to provide any **evidence** or **express findings of fact** as to why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. Further, Applicants assert that the bulk of the Examiner's arguments in the Office Action mailed May 25, 2006 (i.e., pages 9–12), comprise merely allegations of unpredictability in the art.

As a second matter, the United States Court of Appeals for the Federal Circuit has recently made clear the following points regarding the written description required for biotechnological inventions in Capon v. Eshhar (418 F.3d 1349, Fed. Cir. 2005). First, "[t]he descriptive text needed to meet [the written description requirement] varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." Id at 1357. Second, "[t]he written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure"." Id at 1357. Third, "[t]he written description requirement must be applied in the context of the particular invention and the state of the knowledge." Id at 1358. Fourth, "[a]s each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." Id at 1358. Fifth, "[w]hen the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh." Id at 1358.

Additionally, the USPTO has issued guidelines for the examination of patent applications under the 35 USC § 112, first paragraph, written description requirement. These guidelines state that the written description requirement of 35 USC § 112, first paragraph, can be met by

> show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, **functional characteristics when coupled with a known or disclosed correlation**

> **between function and structure**, or some combination of such characteristics.

Guidelines for Examination of Patent Applications under 35 USC § 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001) (emphasis added).

Applicants respectfully note that the nexus of the instant invention was the realization that the expression of a plurality of recombinant proteins from chimeric RNA transcripts could be disrupted by RNAi induced by the action of a single, pre-selected, "universal interfering RNA" (i.e., an siRNA or shRNA), if that universal interfering RNA targeted a commonly shared sequence (i.e., a "universal target RNA," or UtRNA) incorporated into a plurality of chimeric RNA transcripts encoding that plurality of recombinant proteins. Applicants further note that the "fundamental elements" of the invention, include (a) a shared, common UtRNA (which can be located essentially anywhere in the recombinant transcript), and (b) a corresponding universal interfering RNA (UiRNA) that acts by targeting the UtRNA and inducing RNAi – **and that such elements were already available to the skilled artisan at the time the invention was made!**

At this juncture, Applicants would like to respectfully remind the Examiner that the United States Court of Appeals for the Federal Circuit has ruled that "[c]ompliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Enzo Biochem, 323 F.3d at 963 (Fed. Cir. 2002). In view of this ruling, Applicants respectfully remind the Examiner that the pending claims are drawn towards kits for practicing a novel method – and are NOT drawn towards novel compositions of matter such as novel genes, novel segments of DNA, or even novel siRNAs or shRNAs. Consequently, holding the instant specification to the standard of written description required for novel genes, novel segments of DNA, or novel siRNAs or shRNAs is **inappropriate**. As the specification makes amply clear, and, indeed, as the pending claims indicate, known nucleic acids can be used in the claimed kits and methods of the invention, both in the context of UtRNAs and the UiRNAs that target them. In other words, the concept of "RNAi using a universal target" does not necessarily require the development of new nucleic acid

components with novel activities. Instead, it can encompass the use of new combinations of previously known components. (See below.)

State of the Art:

Applicants respectfully assert that the "written description rejection," as presented in the Supplemental Office Action mailed May 25, 2006, selectively ignores the state of knowledge in the relevant art at the time the instant Application was filed. Additionally, the written description rejection fails to recognize that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003); as recited in Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir., August 12, 2005).

Applicants note that at the time the instant Application was filed, skilled artisans were well aware that RNAi was induced by siRNAs and shRNAs with particular, known structures. Further, the instant Application teaches in detail (at page 2, and in Section 7, pages 39 - 41) the general structures of siRNAs and shRNAs required to induce RNAi, and the methods by which they can be created and introduced into cells, tissues or organisms. The specification also provides references to critical and informative publications providing additional teachings, as well as clear documentation as to what was within the purview of the skilled artisan at the time the instant Application was filed.

In addition to these teachings of the specification, the prior art, as indicated above, provided all the necessary elements to create embodiments of the instant invention at the time of filing, and, further, the post-filing art provides proof of concept to demonstrate that the instant invention is (a) workable, and (b) adequately described. Specifically, the prior art contains descriptions of examples of chimeric RNA transcripts comprising a "subject RNA" operably linked to a "target RNA," which do not naturally occur in nature, and which can be targeted for degradation by RNAi with an siRNA or shRNA that corresponds in sequence to at least a portion of the operably linked target RNA, and not the subject RNA. Thus, in essence, the prior art puts skilled artisans in possession of all of the necessary elements to practice the invention. **Importantly, however, the prior art fails to teach that the same siRNA or shRNA can be used to target a plurality of**

chimeric RNA transcripts, each bearing a different subject RNA operably linked to a shared, "universal," target RNA. This discovery, and, indeed, two embodiments of the instant invention, appear in the post-filing art in two independent publications (*See*, Mangeot *et al.*, *Nucleic Acids Res.* 32:e102 (2004), provided to the Office in the IDS filed March 3, 2004; and Campbell and Choy, *Genet. Mol. Res.* 3:282-287 (2004), provided to the Office in the Supplemental IDS filed September 8, 2006).

As **factual evidence** in support of the assertion that the necessary elements required to create an embodiment of the instant invention were available in the art – and thus known to the skilled artisan – prior to the filing of the instant Application, Applicants first note that the instant Application states "For example, the UtRNA can encode enhanced green fluorescent protein, or any other variety of fluorescent protein." (Specification, page 38, lines 10-11.) Applicants next note that in an article published on August 14, 2001, Caplen *et al.*, taught that enhanced green fluorescent protein (EGFP) recombinantly-expressed in mouse embryonic fibroblasts could be effectively knocked down using chemically-synthesized siRNAs corresponding in sequence to the target region comprising nucleotides 122-141 of the EGFP coding sequence (*i.e.,* GCAAGCUGACCCUGAAGUUC). (*See* Caplen *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 98:9742-9747 (2001); provided to the Office in the Supplemental IDS filed September 8, 2006). This same target sequence was also effectively targeted by Donzé & Picard in HeLa cells recombinantly-expressing EGFP, using enzymatically-synthesized siRNA of the same sequence, according their May 15, 2002 publication (*See* Donzé & Picard. *Nucleic Acids Res.* 30:e46 (2002); provided to the Office in the Supplemental IDS filed September 8, 2006).

As further **factual evidence** that these "prior art elements" can be used to practice the methods of the instant invention, Applicants note that these very same prior art elements reappear in an article describing a "new and universal transgene silencing method based on RNA interference," which was published nine months after the filing of the instant Application. (*See* Mangeot *et al.*, *Nucleic Acids Res.* 32:e102 (2004); which was provided to the Office in the IDS filed March 3, 2004). In demonstrating the effectiveness of this method for silencing transgene expression, Mangeot *et al.*, employ an shRNA that targets the exact same 20 nucleotides of the EGFP coding sequence

targeted by Caplen *et al.* and Donzé & Picard. However, in this embodiment of a so-called "universal transgene silencing method," the EGFP target sequence is not present within the context of a transcript that only encodes full-length EGFP (as it was in the studies of Caplen *et al.* and Donzé & Picard), but rather, it is contained within the context of either a bicistronic transcript encoding human thioredoxin and full-length EGFP, or, alternatively, it is embedded, as part of a 25 nucleotide fragment of the EGFP coding sequence, within the 3'-untranslated region of a chimeric RNA transcript encoding human thioredoxin (an embodiment of the instant invention that was schematically depicted in Figure 1 of the instant Application).

In view of these facts, Applicants assert that apprised of the instant specification, a skilled artisan would immediately recognize that (a) essentially any RNA that had previously been effectively targeted by an siRNA or shRNA could potentially serve as a universal target RNA; and (b) the siRNA or shRNA that had effectively targeted that RNA could potentially serve as the universal interfering RNA.Applicants. Applicants further assert that the knowledge of the art, at the time the instant Application was filed, provided a disclosed function (induction of RNAi), that had been sufficiently correlated to a particular, known structure (specific target RNAs, and siRNAs and shRNAs used to target them and induce RNAi). Hence, the teachings of the art, in combination with the teachings of the specification, provide sufficient written description to satisfy the written description requirement under 35 U.S.C. § 112, 1st paragraph, with respect to the claim elements required to create working embodiments the claimed invention.

Improper *prima facie* case for written description rejection:

As noted above, MPEP § 2163.04 states that "**A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description**."

Applicants respectfully assert that the Supplemental Office Action of May 25, 2006 presents no **factual evidence** indicating why a person skilled in the art would not recognize in the Applicants' disclosure, a description of the invention defined by the claims. Further, Applicants assert that the bulk of the arguments in the Office Action merely amount to allegations of unpredictability in the art.

While the Supplemental Office Action presents arguments (on pages 9 through 12) based upon passages from the instant specification addressing the inherent unpredictability in art as it relates to siRNA structure and function, these arguments, respectfully, are not relevant to the claimed invention, and actually lend support to the claims – at least in terms of its utility. Specifically, the Office Action cites several passages from the instant Application in which Applicants have argued that (a) the *a priori* selection of target sequences within gene transcripts to target with siRNAs and shRNAs is problematic, and (b) the *a priori* design of siRNAs and shRNAs to effectively target specific sequences within target gene transcripts is also problematic. Applicants note that the instant invention is designed to specifically address and solve these problems by eliminating the need to (a) select unique target sequences in the subject RNAs of chimeric RNA transcripts, and (b) design specific siRNAs and shRNAs directed towards those selected target sequences, *a priori*. Indeed, the claimed invention encompasses the use of siRNAs and shRNAs that are already known to effectively target a specific target sequence, and takes advantage of the fact that the sequence they target can be incorporated into a plurality of chimeric RNA transcripts having different subject RNAs, thereby making a plurality of subject RNAs susceptible to RNAi induced by a single "universal interfering RNA," which is already known to effectively induce RNAi. Additionally, the specification make clear that:

> "a UtRNA and its corresponding UiRNA can be chosen and tested in advance to ensure that (a) the expression of gene products encoded by recombinant transcripts bearing a UtRNA are effectively silenced by introduction of a corresponding UiRNA, and (b) the silencing observed is specific. Additionally, and advantageously, a UtRNA that functions effectively and specifically in one chimeric RNA transcript, should function equally well in other chimeric RNA transcripts encoding different gene products."

Specification, p. 21, ll. 3-9. Further, as noted above, the prior art provides specific examples of such siRNAs and shRNAs, and their corresponding target RNAs, which can be used in the kits and methods of the instant invention, and have, in fact, been used to create embodiments of the present invention. *See* Mangeot *et al.*, *Nucleic Acids Res.* 32:e102 (2004) and Campbell and Choy, *Genet. Mol. Res.* 3:282-287 (2004).

In summary, Applicants assert that the description provided in the specification constitutes sufficiently detailed, relevant identifying characteristics of the claimed subject matter consistent with *Enzo*, and the USPTO's own "Written Description Guidelines." Further, Applicants assert that the Supplemental Office Action of May 25, 2005 has failed to establish why one of ordinary skill in the art, provided with the descriptions of the specification, combined with the teachings of the prior art, would be unable to recognize the invention defined by the claims. Finally, as stated by the Federal Circuit in Capon v. Eshhar:

> "The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. … When the prior art includes nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. … As each field evolves, the balance evolves between what is known and what is added by each inventive contribution. … It must be borne in mind that, while it is necessary that an applicant for a patent give to the public a complete and adequate disclosure in return for the patent grant, the certainty required of the disclosure is not greater than that which is reasonable, having due regard to the subject matter involved."

Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. August 12, 2005); at 1358 & 1360.

Working Examples, Actual Reduction to Practice, and Recitation of Known Structures are NOT Required to Satisfy the Written Description Requirement:

As noted above, the Supplemental Office Action of May 25, 2006 uses, as justification for the written description rejection, the arguments that the specification provides (a) no specific examples of the invention, and (b) no evidence that the invention has actually been reduced to practice. The Supplemental Office Action also attempts to justify the written description rejection based upon the absence of recitations of specific structures (i.e., nucleotide sequences) for universal siRNAs and shRNAs, and universal target RNAs.

The need – or, more correctly, the lack of need – for working examples, actual reduction to practice, and recitation of known structures, was recently addressed by the United States Court of Appeals for the Federal Circuit in their decision in Falko-Gunter Falkner, *et al.* v. Stephen C. Inglis, *et al.*, No. 05-1324 (Fed. Cir., May 26, 2006). In this

case, which was an appeal from a decision of the Board of Patent Appeals and Interferences in an interference between a patent by Falkner *et al.* (5,770,212; the Falkner '212 patent) and a patent application by Inglis *et al.* (08/459,040; the Inglis '040 application), the Federal Circuit resoundingly affirmed that neither working examples, nor actual reduction to practice, nor nucleotide or amino acid sequences of known structures, are required to meet the written description requirement.

Specifically, in light of the facts presented in the case, the Federal Circuit, in its precedential opinion, held:

> (1) examples are not necessary to support the adequacy of a written description, (2) the written description standard may be met … even when actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

Falko-Gunter Falkner, *et al.* v. Stephen C. Inglis, *et al.*, No. 05-1324 (Fed. Cir., May 26, 2006); Section II.C., p. 14.

Furthermore, with regard to the requirement for examples of the invention in a specification, the Federal Circuit noted in Falkner (No. 05-1324 (Fed. Cir., May 26, 2006); Section II.C.1., p. 14) what they had previously explained in LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.:

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

Id. 424 F.3d 1336, 1345 (Fed. Cir. 2005)

With regard to the requirement for evidence of actual reduction to practice in a specification, the Federal Circuit reiterated in Falkner that "an actual reduction to practice is not required for written description," further explaining that "to the extent that written description requires a showing of "possession of the invention," …Pfaff [v. Wells Elecs.,

525 U.S. 55, 66 (1998)] makes clear that an invention can be "complete" even where an actual reduction to practice is absent." Falko-Gunter Falkner, *et al.* v. Stephen C. Inglis, *et al.*, No. 05-1324 (Fed. Cir., May 26, 2006); Section II.C.2., pp. 14 & 15.

Finally, with regard to the requirement for recitation of known macromolecular structures, the Federal Circuit observed in Falkner that "it is the binding precedent of this court that Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is know in the prior art. … Thus, "[w]hen the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh." The Federal Circuit concluded by stating: "Accordingly we hold that where … accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences … satisfaction of the written description requirement does not require either the recitation or incorporation by reference … of such genes and sequences. Falko-Gunter Falkner, *et al.* v. Stephen C. Inglis, *et al.*, No. 05-1324 (Fed. Cir., May 26, 2006); Section II.C.3., pp. 16 - 18.

In view of the precedential opinion set forth in Falko-Gunter Falkner, *et al.* v. Stephen C. Inglis, *et al.*, No. 05-1324 (Fed. Cir., May 26, 2006), Applicants respectfully submit that written description requirement, as regards specific examples of the invention, actual reduction to practice of the invention, and description of nucleotide sequences of elements of the invention, has been met by the specification, as filed.

With regard to the allegation that the specification does not allow the skilled artisan to recognize that applicants were in possession of the "the entire genus of universal interfering siRNAs, shRNAs, and expression vectors expressing said siRNAs and shRNAs targeting all possible universal target RNAs," Applicants note that the USPTO's own Written Description Guidelines indicate that the written description requirement of 35 USC § 112, first paragraph, can be met by

> Show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics … i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph, "Written Description" Requirement, 66 Fed.Reg. 1099, 1106 (Jan. 5, 2001).

In the instant case, apart from the specific nucleotide sequences involved (i.e., the primary structures), the siRNAs, shRNAs and target RNAs encompassed by the claims have both structural and functional characteristics that are known from the prior art, and are clear to the artisan skilled in the practice of RNAi. Additionally, the specification provides: "the siRNAs that are most effective in mammalian cells are duplexes composed of two complementary 21 nucleotide single-stranded RNAs that anneal to form a duplexed region of 19 basepairs and single-stranded overhangs of 2 nucleotides at their 3' ends." Specification, p. 16, ll. 7-10. Thus, Applicants respectfully assert that the have shown their invention to be complete by disclosure of "sufficiently detailed, relevant identifying characteristics … i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In view of the Federal Circuit's recent decisions in Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005), and Falko-Gunter Falkner, et al. v. Stephen C. Inglis, et al., No. 05-1324 (Fed. Cir. 2006), as well as the USPTO Written Description Guidelines and Training Materials, and the arguments presented above, Applicants respectfully assert that the instant specification provides more than adequate written description of the claimed invention under 35 USC § 112, first paragraph. Accordingly, Applicants request that written description rejection under 35 USC § 112, first paragraph, be withdrawn.

As a final request, while considering the arguments presented above, Applicants respectfully ask the Examiner to carry out the following mental exercise: Go back in time to October 6th, 2003 (the day the instant Application was filed) and put yourself in the labcoat of an artisan skilled in the art of RNA interference; an artisan who has already succeeded in knocking down the expression of a gene product (for example, EGFP) by RNAi, in cultured cells. Pretend that your supervisor gave you a copy of the instant patent application and asked you to read it with the aim of using the disclosed methods and kits in the laboratory's research program. Now ask yourself: Knowing what you know about inducing RNAi with specific siRNAs, and having read the instant

application, would you then possess sufficient knowledge of the claimed invention to set about using it in your own research efforts? Would you understand how to knock down the expression of a plurality of gene products with a single "universal interfering RNA" directed to a shared "universal" target sequence in a plurality of chimeric RNA transcripts? Would you not recognize in the disclosure of the instant application, a description of the invention defined by the claims? Would you not recognize methods and kits that you could immediately put to use in your own research efforts? If so, then that patent application your supervisor asked you to read clearly met the written description requirement of 35 USC § 112, first paragraph.

CONCLUSIONS

Claims 16 through 34 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact the undersigned via his direct office line (801-883-3463). Additionally, should either claim 16 or 18, or both, be found to be allowable, Applicant respectfully requests rejoinder and examination of withdrawn process (method) claims (i.e., claims 1-15), in accordance with the provisions of MPEP § 821.04.

A petition for a one-month extension of time for the filing of this response is being filed concurrently herewith. Provisions for the payment of the necessary fee have been made in the petition. Therefore, it is believed that no other extension of time, or any additional fees are due with this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees, or credit any over payment, to Deposit Account no. **50-1627**.

Respectfully submitted,

/Herbert L. Ley/
Herbert L. Ley III, Ph.D. 53,215

September 25, 2006

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EXHIBIT A

1: Biotechniques. 1994 Apr;16(4):730-5.

Immunoaffinity purification of FLAG epitope-tagged bacterial alkaline phosphatase using a novel monoclonal antibody and peptide elution.

- Brizzard BL,
- Chubet RG,
- Vizard DL.

Eastman Kodak Company, New Haven, CT.

The FLAG epitope is an eight amino acid peptide (AspTyrLysAspAspAspAspLys) that is useful for immunoaffinity purification of fusion proteins. A monoclonal antibody (anti-FLAG M1) that binds the FLAG epitope in a calcium-dependent manner and requires an N-terminal FLAG sequence has been described previously. We describe the use of a second anti-FLAG monoclonal antibody (anti-FLAG M2) in immunoaffinity purification of N-terminal Met-FLAG and C-terminal FLAG fusion to bacterial alkaline phosphatase. Although binding of an anti-FLAG M2 monoclonal antibody to the FLAG epitope is not calcium-dependent, bound fusion proteins can be eluted by competition with FLAG peptide.

PMID: 8024796 [PubMed - indexed for MEDLINE]